A thermodynamic force generated by chemical gradient and adsorption reaction

Takeshi Sugawara[1] and Kunihiko Kaneko[1,2]

[1]*Department of Basic Science, Graduate School of Arts and Science,*
The University of Tokyo, 3-8-1, Komaba, Meguro, Tokyo 153-8902, Japan
[2]*Complex Systems Biology Project, ERATO, JST, Komaba, Meguro-ku, Tokyo, Japan*

Biological units such as macromolecules, organelles, and cells are directed to a proper location under gradients of relevant chemicals. By considering a macroscopic element that has binding sites for a chemical adsorption reaction to occur on its surface, we show the existence of a thermodynamic force that is generated by the gradient and exerted on the element. By assuming local equilibrium and adopting the grand potential from thermodynamics, we derive a formula for such a thermodynamic force, which depends on the chemical potential gradient and Langmuir isotherm. The conditions under which the formula can be applied are demonstrated to hold in intracellular reactions. The role of the force in the partitioning of bacterial chromosome/plasmid during cell division is discussed.

Introduction   Biological entities such as cells, organelles, and macromolecules often move to a proper location under an external gradient of chemicals. In the chemotaxis of a cell, the process by which an organism senses the presence of an external chemical and responds to it has been elucidated in depth. However, such coordinated motion is not limited to the organism level. In recent studies, it has been revealed that such directional motion under chemical gradients/localizations plays an important role in organization at an intracellular level [1], e.g., microtubule guidance under the RanGTP gradient [2] or Stathmin gradient [3], actin nucleation under the IcsA gradient on the outer membrane of the pathogen *Shigella flexneri* (actin comet)[4], bacterial chromosome/plasmid DNA partitioning by a Par system [5, 6, 7, 8, 9, 10, 11, 12], and several transport processes by scaffold proteins. However, the general mechanism by which organelles or macromolecules demonstrate coordinated motion under an intracellular gradient/localization is yet to be determined.

The pattern formation process of chemical concentrations under a non-equilibrium condition, first reported for a macroscopic morphogenesis[14], has recently been observed at an intracellular level as well, and its relevance to intracellular organization processes has been demonstrated in bacterial plasmid DNA partitioning Par system[8][10], Min system for determining the plane of cell division in bacteria [13], etc. They discussed how positional information given by the chemical concentration gradient/localization is obtained and stored with the mechanism. However, there are few studies on how the coordinated motion or transport of organelles or macromolecules caused by chemical gradient/localization is sustained under non-equilibrium conditions.

In the present paper, we present a physical mechanism of such directed motion by showing that under a chemical gradient corresponding to a reaction, a macroscopic element consisting of a number of reaction sites is generally subject to a force. By representing this element as a scaffold for the adsorption of a chemical, we derive a general formula for a force generated by a chemical potential gradient. In the derivation, we introduce the grand potential in thermodynamics for an open system [17] and apply the second law of thermodynamics. Irrespective of the nature of the molecules, the force acts to decrease the grand potential when a chemical potential gradient exists. Then, the element moves in a direction such that the chemical potential increases. A formula is obtained by assuming that the reaction process reaches equilibrium faster than the motion of the element and by extending the minimization of free energy to include the contact with a particle bath with a given chemical gradient. We propose that this force generates a general mechano-chemical coupling driven by the chemical potential gradient through an adsorption reaction. The proposed formula is valid since the work extracted by the gradient force dominates the thermal energy fluctuation. By examining whether this condition is satisfied in the intracellular reaction process, we discuss the possible role of this force in the partitioning dynamics of bacterial chromosome/plasmid for cell division.

Chemical gradient force   Now, consider organelles or macromolecules that have a number of binding sites for reactions to occur on their surface; for example, nucleoprotein complexes (NCs) have several promoter sites to bind transcription factors, etc. Let us model these biological elements simply as "beads" with several reaction sites to which the corresponding molecules attach, as shown in Fig.1. The bead is placed at $r = \xi$ and moves in a d-dimensional space $r \in R^d$ (d=1,2,3). We consider an isothermal process that is homogeneous over space at a given temperature T, whereas we consider a chemical bath with a spatially dependent concentration $x(r)$ of a chemical X, or equivalently, the corresponding chemical potential $\mu(r)$. This gradient is assumed to be sustained externally. This chemical is attached to the binding sites B on the bead and thus forms a complex Y (Fig.1), as given by the reaction $X(\xi) + B \leftrightarrows Y$. The molecular number of the complexes on the bead is denoted by N_y. Note that the "bead" here is defined as a macroscopic entity compared to the molecule X. To develop local-equilibrium conditions, we make the following assumptions. The "adsorption" reaction on the bead is considered to be a macroscopic event and N_y is a molec-

ular number averaged over a much longer timescale than the microscopic timescale of the reaction. Further, the bead is assumed to move sufficiently slowly so that local chemical equilibrium of the above reaction can be assumed to exist at each position $r = \xi$. In other words, the timescales of diffusion of X molecules τ_{diff} and adsorption reaction τ_{adsorb} are much smaller than the timescale of the motion of the bead τ_{bead}: $\tau_{diff}, \tau_{adsorb} \ll \tau_{bead}$. As long as the bead is in motion, it is maintained in equilibrium with the reservoir at $r = \xi$.

With the assumption of the existence of local equilibrium, we can apply thermodynamics with spatially dependent thermodynamic variables. Indeed, at each position ξ, the reaction process is described by the familiar classical Langmuir adsorption theory [15][16]; Note that the theory has been successfuly applied to DNA-protein binding equilibrium [15]. The grand potential in thermodynamics at each position is given by $\Omega(\xi) = F(\xi) - y\mu(\xi)$, $d\Omega(\xi) = dF(\xi) - d(y\mu(\xi)) = -yd\mu(\xi)$, where $y = \frac{N_y}{V}$ (V : volume of the bead), $F(\xi)$ is the Hermholtz free energy, and $dF(\xi) = \mu(\xi)dy$ [17][22].
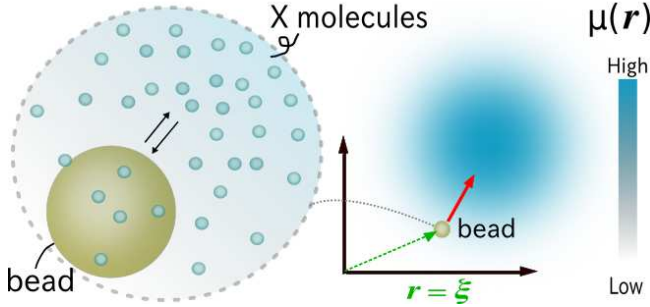

Figure 1: Schematic representation of our system. A "bead" is placed at $r = \xi$ and moves in a d-dimensional space (d=1,2,3). The adsorption reaction $X(\xi) + B \leftrightarrows Y$ occurs on the surface of the bead.

Now, consider a virtual displacement for the position of the bead $r = \xi$. Under an infinitesimal displacement $\xi \to \xi + d\xi$, the change in the grand potential is $d\Omega(\xi) = -yd\mu(\xi) = -y\nabla\mu(\xi)\cdot d\xi$. In other words, the position of the bead ξ is adopted as an effective independent variable instead of the chemical potential $\mu(\xi)$. Then, ξ is the work coordinate, while $-y\nabla\mu(\xi)$ is the force exerted on the bead by the external world balanced by the force exerted on the bead due to reservoir chemical potential distribution $\mu(r)$. The chemical gradient force generated by the reservoir acts on the bead per unit volume of the bead:

$$\boldsymbol{f}_{chem} = -\boldsymbol{\nabla}\Omega(\xi) = y\boldsymbol{\nabla}\mu(\xi) \tag{1}$$

This expression is interpreted as follows: consider a quasi-static infinitesimal displacement $d\xi$. Then, from the change in the grand potential, the maximum work that the system does on the external world through the

reservoir is $d'W = y\boldsymbol{\nabla}\mu(\xi)\cdot d\xi$. By considering that this work is due to the force that the reservoir exerts on the bead, as $d'W = \boldsymbol{f}_{chem}\cdot d\xi$, the force formula eq.(1) is obtained. In other words, without an externally applied force, ξ evolves spontaneously so that $\Omega(\xi)$ monotonically decreases, that is, $d\Omega(\xi) < 0$ [23]. When we consider the overdamped system, where the kinetic energy of the bead is negligible, the equation of motion is given by $-\dot{\Omega}(\xi) = T\sigma(\xi) > 0$, where $\sigma(\xi) := \frac{d_{ir}S}{dt}(\xi)$ is the entropy production of the system. The above equation of motion is rewritten as $\gamma\,\dot{\xi} = -\boldsymbol{\nabla}\Omega(\xi) = y\boldsymbol{\nabla}\mu(\xi)$, when there is dissipation due to friction, assumed to be proportional to the velocity with the proportionality constant γ—the friction coefficient per unit volume of the bead.

Now, consider the condition for local chemical equilibrium. Because $c = y + b = const.$, the dissociative constant is defined as $K := \frac{k_-}{k_+} = \frac{x(\xi)b}{y}$, where y is given by the Langmuir isotherm $y = y(x(\xi)) = c\frac{x(\xi)}{K+x(\xi)}$ [24]. If we consider cooperative adsorption of n chemicals on the bead: $nX(\xi) + B \leftrightarrows Y$, the isotherm for the adsorption is given as $y(x(\xi)) = c\frac{x(\xi)^n}{K^n+x(\xi)^n}$, where n determines a Hill coefficient. Therefore, the equation of motion is written as

$$\gamma\,\dot{\xi} = c\frac{x(\xi)^n}{K^n + x(\xi)^n}\boldsymbol{\nabla}\mu(\xi) \tag{2}$$

Equation (2) is a general formula for the motion of an element that has a number of binding sites for chemical adsorption under the gradient of corresponding chemical potential. The theoretical description of the motion of the bead is somewhat an extended form of Langmuir adsorption theory. Because of this force, the bead moves in a direction such that the grand potential Ω, the thermodynamic potential for open systems, is decreased; this decrease follows from the second law of thermodynamics. Accordingly, the bead moves in the direction of increasing chemical potential.

In our formulation, the chemical potential $\mu(r)$ is regarded to be equivalent to the external potential field for bead motion, similar to the magnetic field in which a magnetic dipole is placed. Indeed, the magnetic force that acts on the dipole placed in the magnetic field gradient acts in the direction of increasing magnetic field strength.

When an additional external potential field $E(r)$ such as elastic energy is applied to the bead, the relation $dF(\xi) = dE(\xi) + \mu(\xi)dy(\xi)$ holds from the first law of thermodynamics. Accordingly, the grand potential of the system given by $\Omega(\xi) = F(\xi) - y(\xi)\mu(\xi)$ satisfies $d\Omega(\xi) = dF(\xi) - d(\mu(\xi)y(\xi)) = dE(\xi) - y(\xi)d\mu(\xi)$. Further, by taking into account thermal fluctuation, the equation of motion of the system is given by

$$\gamma\,\dot{\xi} = -\boldsymbol{\nabla}E(\xi) + y(\xi)\boldsymbol{\nabla}\mu(\xi) + \boldsymbol{\eta}(t) \tag{3}$$

with $\langle\boldsymbol{\eta}(t)\rangle = 0$, $\langle\boldsymbol{\eta}(t)\cdot\boldsymbol{\eta}(t')\rangle = 2d\gamma k_BT\delta(t - t')$. Note that the equation is obtained as an extended form of

a conventional one with the Hermholtz free energy as the thermodynamic potential for a closed system. It is straightforward to further extend the present formula to include a case involving multiple beads and multiple components with interactions among the beads.

An example We consider a simple toy model as an example of eq.(3). We assume that a bead placed at $r = \xi$ is balanced at $r = 0$ in a 1-dimensional space r by a restoration force, which is produced by a linear spring and represented by a harmonic potential $E(\xi) = \frac{a}{2}\xi^2$. The concentration of the chemical that reacts with the bead is assumed to be sustained and is given by $x(r) = x_s \exp(\lambda(r - r_s))$, where $x_s = x(r_s)$ is the concentration of X at $r = r_s$, while the corresponding chemical potential is given by $\mu(r) = \bar{\mu} + k_B T \ln x(r)$. Here, $\bar{\mu}$ is the standard chemical potential. Then, by using eq.(3) without considering thermal fluctuation, the equation of motion of the bead is obtained as $\gamma \dot{\xi} = y(\xi)\frac{d\mu}{dr}(\xi) - \frac{dE}{dr}(\xi) = \lambda k_B T c \frac{x(\xi)^n}{K^n + x(\xi)^n} - a\xi$. Here, γ, c, K, a are the frictional coefficient, maximum adsorption concentration, dissociative constant, and spring constant, respectively. This equation can be rewritten as $\gamma \dot{\xi} = \frac{A}{1 + B\exp(-n\lambda(\xi - r_s))} - a\xi$ with $A = \lambda k_B T c$, $B = \left(\frac{K}{x_s}\right)^n$. The solution of the equation shows bistability as it includes a sigmoid function. Thus, under appropriate parameter regions, as x_s, which is taken as a control parameter, is increased, the model thus undergoes two-fold bifurcations from monostable fixed points to bistable ones and then back to monostable states. This implies that the gradient force determines the stable fixed position of the bead. This toy model can be used to explain how the stable position of an organella undergoes bifurcation to a new location as the chemical concentration increases. An example may be seen in bacterial chromosome/plasmid partitioning, as will be discussed later.

Conditions for chemical gradient force (i) : relationships among timescales The grand canonical description with local chemical equilibrium can be adopted only in certain conditions. The following relationships among timescales must exist: (1) the timescale of adsorption τ_{adsorb} must be shorter than that of bead motion τ_{bead} in order for the adsorption reaction to reach equilibrium (approximately) before the bead moves, and (2) the timescale of bead motion must be much larger than that of the diffusion of the chemical adsorbed on the bead, i.e., $\tau_{bead} \gg \tau_{diff}$. This condition is necessary to assume macroscopic motion of the bead under the chemical gradient, which itself diffuses in space. In the living cells of particular interest, the molecular number is not so large that the instantaneous chemical concentration fluctuates greatly. Hence, in order to determine the macroscopic concentration, the temporal average of the concentration of molecules over the diffusion timescale must be calculated [18], and hence, the above condition is important.

Condition (ii): dominance of chemical gradient force over thermal fluctuation As long as the above conditions are satisfied, on an average, the gradient force acts in the direction in which the chemical potential increases, regardless of thermal fluctuation. However, the gradient force must be larger than thermal noise in order for the force to act effectively without the need for long-time averaging to remove fluctuation. This establishes the following condition: the work done by the force must be larger than the thermal energy, i.e., $-V \int_{\boldsymbol{\xi}_0}^{\boldsymbol{\xi}} d\boldsymbol{\xi}' y(\boldsymbol{\xi}') \boldsymbol{\nabla}\mu(\boldsymbol{\xi}') \gtrsim k_B T$ for directional motion from $\boldsymbol{\xi}_0$ to $\boldsymbol{\xi}$ [25]. In the case of one-dimensional motion from $r = 0$ to L, the above condition for the work is rewritten as follows: the concentration and chemical potential of chemical X are obtained as $x(r) = x_0 \exp(-\frac{r}{r_c})$ and $\mu(r) = \bar{\mu} + k_B T \ln x(r)$, respectively. Here, x_0 gives the highest concentration at $r = 0$. Then, the above inequality is written as $\frac{N_c}{r_c} \int_0^L d\xi \frac{x_0^n e^{-n\frac{\xi}{r_c}}}{K^n + x_0^n e^{-n\frac{\xi}{r_c}}} \gtrsim 1$ with $N_c = Vc$. A straightforward calculation leads to the inequality $\frac{N_c}{n} \ln \left(\frac{1 + \left(\frac{x_0}{K}\right)^n}{1 + \left(\frac{x_0}{K}\right)^n \exp\left(-n\frac{L}{r_c}\right)} \right) \gtrsim 1$. We can rewrite the above inequality in the form $\frac{x_0}{K} \gtrsim \left(\frac{\exp(\frac{n}{N_c}) - 1}{1 - \exp\left(-n\left(\frac{L}{r_c} + \frac{1}{N_c}\right)\right)} \right)^{\frac{1}{n}}$, with the additional condition $N_c > \frac{r_c}{L}$ [26]. Note that the the lower bound on $\frac{x_0}{K}$ decreases with $\frac{L}{r_c}$ and N_c, and the formula is valid over a wide range of $\frac{x_0}{K}$.

An application Now, we consider applications of the chemical gradient force within a cell. As an example, consider the partitioning of chromosome/plasmid in bacteria during cell division [5, 6, 7, 8, 9, 10, 11, 12]. Here, the bead corresponds to the chromosome/plasmid on which the relevant protein (X in the model) binds to form a nucleoprotein complex (NC) (Y in the model) that is important for partitioning. For the application, the above-mentioned condition on the timescales, $\tau_{diff}, \tau_{adsorb} \ll \tau_{bead}$ has to be satisfied. In general, the timescale of protein binding equilibrium on bacterial DNA τ_{adsorb} is at most $\tau_{adsorb} \lesssim 1(s)$. In [19], it has been suggested that the segregation of chromosomes is spatially restricted and the diffusion coefficient D is estimated as $O\left(10^{-4} \sim 10^{-5}\right)$. The size of NC, a, is assumed to be on the order of $a \sim 50(nm)$, so that τ_{bead} is estimated as $\tau_{bead} \sim \frac{a^2}{D} \sim \frac{0.05^2}{10^{-4}} \sim 25(s)$. Similarly, τ_{diff} is estimated as $\tau_{diff} \sim \frac{a^2}{D_x} \sim 10^{-3}(s)$, where D_x is the diffusion coefficient of proteins within cytoplasm and is roughly estimated as $D_x \sim 3.0(\mu m^2/s)$ (according to [20]). Therefore, $\tau_{diff} \ll \tau_{adsorb} \ll \tau_{bead}$ is satisfied for our formula.

To be specific, the replicated bacterial chromosomes/plasmids are actively partitioned to daughter cells by a Par system [5, 6, 7, 8, 9, 10, 11, 12]. The most ubiquitous partitioning system is the *parABS* system. Before cell division, daughter chromosomes/plasmids are precisely segregated by ParA dynamic localization along with the associated ParA-NC interaction. It has been suggested that ParA localization pulls chromosomes[7] or at least guides plasmid[12], but how ParA generates the

driving force for chromosome/plasmid segregation has not been elucidated yet. Now, ParA is regarded as X, NC (to be precise, ParB-$parS$ NC mediated by ParA) as Y in our model [27]; this driving force is naturally explained by the chemical gradient force. To confirm the validity of our formula, we simply consider the steady concentration distribution of ParA to be $x(r) = x_0 \exp(-\frac{r}{r_c})$ within $[0, L]$ [6, 7]. We then take $n = 2$, because ParA cooperatively binds DNA [21] and choose $K = 0.3(\mu M)$ on the basis of recent data obtained by [21]. Although the precise number of ParA that binds DNA around NC is unknown, $N_c \sim 10$ is a natural choice since many ParA are suggested to bind DNA around NC. The localization scale r_c of ParA localization is also not precisely known and could vary across bacterial species. By taking $\frac{L}{r_c} \sim 5$ as an order estimate from [6, 7], we obtain $\frac{x_0}{K} \gtrsim 0.5$. Active protein binding generally occurs when a reasonable concentration $x_0 \sim K$ is reached, where $\frac{x_0}{K}$ is sufficiently large to satisfy the above inequality. Therefore, the chemical gradient force dominates the thermal fluctuation if $x_0 \gtrsim K$. Although the mechanism of ParA localization could depend on the species, the estimate suggests that the force plays a significant role in the partitioning of plasmid/chromosome, independent of the specific molecular mechanisms. Further, we note that the above-mentioned "spring toy model" under a gradient is applicable to the partitioning problem and may help explain the bifurcation of plasmid/chromosome in cell division with the change in ParA localization.

Of course, the biological ParA distribution is more complicated. Although the application mentioned here assumes ParA steady distribution, the distribution sometimes shows pole-to-pole oscillation [12] and regular patterns to form regular spacing of a few plasmid foci [10, 11]. Still, our theory is applicable to the time-varying distribution, because the force derived here leads to directional motion toward the ParA foci. Indeed, the directional motion toward ParA focus has been suggested in [12]. Furthermore, the present gradient force is applicable to reaction-diffusion system so that the plasmid is located according to the chemical concentration pattern.

Discussion In this study, we have demonstrated that when a chemical concentration gradient exists, a macroscopic element that acts as a scaffold for the absorption of some chemical is generally subject to a thermodynamic force, and it moves in the direction of increasing chemical potential. The force is generated in accordance with the second law of thermodynamics, as represented by the decrease in the grand potential in thermodynamics under a given gradient; thus, this force acts independent of the specific molecular mechanism. The gradient force is expected to provide a novel perspective on mechanochemical coupling. We have derived a general formula for the magnitude of the force and presented a few conditions necessary for this formula to be valid. The conditions are shown to be satisfied for the intracellular motion of macromolecules or organelles under a suitable chemical gradient, and the force is clearly shown to be larger than the thermal fluctuation force. To be specific, we have discussed the application of this formula to bacterial partitioning systems in cell division. Considering the generality of our formulation, the chemical gradient force is expected to be a universal guiding principle in intracellular organization.

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[22] Here we assume that the gradient of X is not influenced by the adsorption reaction. This assumption is valid if $x(\boldsymbol{\xi}) \gg y$.

[23] The variational principle for the grand potential Ω can be

proved by the principle of maximum work in an isothermal process. See Supplementary Information for a detailed derivation.

[24] In terms of statistical mechanics, the Langmuir isotherm should be obtained as a function of the chemical potential $\mu(\boldsymbol{r})$ at $\boldsymbol{r} = \boldsymbol{\xi}$. We can derive the representation as a function of $\mu(\boldsymbol{r})$ when $\mu(\boldsymbol{r})$ is that for a dilute solution, i.e., $\mu(\boldsymbol{r}) = \bar{\mu} + k_B T \ln x(\boldsymbol{r})$. Here, $\bar{\mu}$ is the standard chemical potential.

[25] This inequality is also derived from the steady solution of the Smoluchowski equation. For one-dimensional motion, the steady-state distribution of ξ is given by $P(\xi) = A \exp\left(-\frac{W(\xi)}{k_B T}\right)$. Here, A is a normalized factor and $W(\xi) = -V \int_0^\xi d\xi' y(\xi') \nabla \mu(\xi')$. If the position ξ_c that satisfies $W(\xi_c) \sim k_B T$ is smaller than the system size L, the distribution is concentrated toward higher chemical potentials and the gradient force dominates the thermal fluctuation. Then, the inequality in the text is obtained.

[26] We can also represent the condition in terms of the average concentration x_{av} for $[0, L]$.

[27] The Par system consists of three components: DNA binding protein ParB, ATPase ParA, and centromere-like site $parS$. ParB binds $parS$, spreads along DNA, and forms a large NC around $parS$. ParA can nonspecifically bind to DNA and interact with the ParB-$parS$ NC [5, 6, 7, 8, 9, 10, 11, 12].

Supplementary information

Proof of the variational principle for grand potential with the principle of maximum work — It is well known that the grand potential is a thermodynamic potential in terms of natural variables T, μ, and surface area; extensive studies such as those on adsorption and capillary phenomenon involve this potential. However, to the best of our knowledge, there is no proof of the variational principle for the grand potential, particularly when μ varies; nevertheless, this potential is closely connected by the Legendre transformation to the other thermodynamic potentials for which the existence of variational principles has been proven. It seems to be because

- standard thermodynamic operation involves extensive variables but not intensive ones in order to obtain work from a thermodynamic system.

This is not the case in this study because μ can be controlled by changing the d-dimensional position of the thermodynamic system (d=1,2,3). Therefore, we will derive the variational principle for the grand potential on the basis of the principle of maximum work.

Consider a thermodynamic system composed of a bead with a surface as shown in (Fig.1). The bead is placed at $\boldsymbol{r} = \boldsymbol{\xi}$ and moves in a d-dimensional space $\boldsymbol{r} \in \boldsymbol{R}^d$ (d=1,2,3). It makes contact with a heat-particle bath (reservoir) with homogeneous temperature $T(\boldsymbol{r}) = T$ and chemical potential $\mu(\boldsymbol{r})$ (concentration $x(\boldsymbol{r})$) at $\boldsymbol{r} = \boldsymbol{\xi}$ for a chemical X. The chemical is adsorbed on the surface of the bead B and forms a complex Y with it (Fig.1): $X(\boldsymbol{\xi}) + B \leftrightarrows Y$. The concentration on the bead is denoted by y.

Assume that the bead is in equilibrium with the reservoir at $\boldsymbol{r} = \boldsymbol{\xi}$ and it is maintained in equilibrium during its motion. Therefore, the temperature and chemical potential of the system are always balanced by those of the reservoir, that is, $T_{system} = T, \mu_{system} = \mu(\boldsymbol{\xi})$. Note that we assume the existence of local equilibrium, where several thermodynamic variables can be defined in the d-dimensional space.

The precise definition of the grand potential is as follows:

$$\Omega(T, \mu) := \min_y \left[F(T, y) - y\mu \right]$$

This is the precise representation for the Legendre transformation from $F(T, y)$, the Helmholtz free energy in terms of natural variables (T, y), to $\Omega(T, \mu)$ in terms of natural variables (T, μ); mathematically, this implies that y must be determined as a function of T, μ, so that $F(T, y) - y\mu$ is minimized when y is varied with fixed T, μ. The determined y^* and $F(T, y^*) - y^*\mu$ are identical to the Langmuir isotherm and the grand potential, respectively.

The principle of maximum work represents the second law of thermodynamics in terms of the work obtained by an isothermal process. First, we assume that the principle of maximum work is applicable, and we vary y while keeping T constant:

$$W_{max}(T, y_1 \to y_2) = F(T, y_1) - F(T, y_2)$$

When y is quasistatically changed from y_1 as a function of μ_1 to *any* y_2 by moving the position of the bead from $\boldsymbol{\xi}_1$ to $\boldsymbol{\xi}_2$ via the force $\boldsymbol{f}$ exerted by the external world (This force was balanced by the chemical gradient force or forces from the other potential fields, such as mechanical or magnetic forces.), the work $W(T, \mu_1 \to \mu_2)$ in terms of natural variables T, μ obtained by changing μ from μ_1 to μ_2 and keeping T fixed, which is the work performed by the system on the external world and is given as follows:

$$W(T, \mu_1 \to \mu_2) = -\int_{\boldsymbol{\xi}_1}^{\boldsymbol{\xi}_2} \boldsymbol{f} \cdot d\boldsymbol{\xi}$$

$$= W_{max}(T, y_1 \to y_2) - \left(-\int_{y_1\mu_1}^{y_2\mu_2} d\left(y\mu\right) \right)$$

The first term represents the total work that the system can perform, and the second term represents the work that it must perform on the reservoir for the change $y_1 \to y_2$, i.e., the work that it cannot perform on the external world. We can interpret the latter work as follows: the potential energy of the system is $-y(\boldsymbol{\xi})\mu(\boldsymbol{\xi})$ at $\boldsymbol{r} = \boldsymbol{\xi}$ when it is placed in a potential field $\mu(\boldsymbol{r})$, similar to a situation in which a dipole is placed in the magnetic field generated by a magnet, as discussed below. Furthermore, the former (latter) work is related to the interactions that result in heat (chemical X) exchange with the reservoir, respectively. The interactions are represented by changing y through $\boldsymbol{\xi}$ while T remains fixed. The essential point is that only the latter work yields information on the system as an open system.

We consider maximizing $W(T, \mu_1 \to \mu_2)$ by changing y_2 determined arbitrarily so far and then determining it as a function of T, μ_2. The maximum work is expressed in terms of natural variables T, μ as $W_{max}(T, \mu_1 \to \mu_2)$. We obtain the maximum work in terms of natural variables (T, μ) as follows:

$$W_{max}(T, \mu_1 \to \mu_2) = \max_{y_2} W(T, \mu_1 \to \mu_2)$$

$$= \max_{y_2} \left[W_{max}(T, y_1 \to y_2) + y_2\mu_2 - y_1\mu_1 \right]$$

$$= F(T, \mu_1) - y_1\mu_1 - \min_{y_2} \left[F(T, \mu_2) - y_2\mu_2 \right]$$

$$= \Omega(T, \mu_1) - \Omega(T, \mu_2)$$

That is, the maximum work that the system assigned $(T, \mu(\boldsymbol{\xi}))$ by the reservoir $(T, \mu(\boldsymbol{r}))$ at $\boldsymbol{r} = \boldsymbol{\xi}$ can perform on the external world is obtained by calculating the decrease in the grand potential $\Omega(T, \mu(\boldsymbol{\xi}))$.

Next, we consider the situation in which the force $\boldsymbol{f}$ exerted by the external world vanishes ($\boldsymbol{f} = \boldsymbol{0}$) and the change $\mu \to \mu'$ occurs spontaneously. In this case, $W(T, \mu \to \mu') = 0$ because $\boldsymbol{f} = \boldsymbol{0}$.

$$\therefore W_{max}(T, \mu \to \mu') \geq W(T, \mu \to \mu') = 0$$

$$\Leftrightarrow \Omega(T, \mu') - \Omega(T, \mu) \leq 0$$

Because the start state (T, μ) can be chosen arbitrarily, the grand potential monotonically decreases till the end state (T, μ') under local equilibrium is reached. If (T, μ') is in equilibrium, the grand potential reaches a minimum at this state.

For an infinitesimal displacement $\boldsymbol{\xi} \to \boldsymbol{\xi} + d\boldsymbol{\xi}$, the following inequality is satisfied:

$$d\Omega(T, \mu) = \boldsymbol{\nabla}\Omega(T, \boldsymbol{\xi}) \cdot d\boldsymbol{\xi} < 0$$

Therefore, for a displacement per unit time $\dot{\boldsymbol{\xi}}$,

$$\dot{\Omega}(T, \boldsymbol{\xi}, \dot{\boldsymbol{\xi}}) = \boldsymbol{\nabla}\Omega(T, \boldsymbol{\xi}) \cdot \dot{\boldsymbol{\xi}} < 0$$

Because the change in the grand potential is completely dissipated due to $W(T, \mu \to \mu + d\mu) = 0$ if the kinetic energy of the bead is negligible, the following inequality is satisfied:

$$-\dot{\Omega}(T, \boldsymbol{\xi}, \dot{\boldsymbol{\xi}}) = T\sigma(\dot{\boldsymbol{\xi}}) > 0$$

$\sigma(\dot{\boldsymbol{\xi}})$ is the entropy production of the system. Thus, we can show that the variational principle applies to the grand potential of the system.

If the dissipation in the system is only caused by friction due to the motion of the bead, the following relation is satisfied for the power that the system does for friction $\dot{W}_{fr}(\dot{\boldsymbol{\xi}})$.

$$-\dot{\Omega}(T, \boldsymbol{\xi}, \dot{\boldsymbol{\xi}}) = T\sigma(\dot{\boldsymbol{\xi}}) = \dot{W}_{fr}(\dot{\boldsymbol{\xi}}) > 0$$

Comparison with Gibbs free energy of magnetic dipole moment — For understanding the work that the system must perform on the reservoir as discussed above, it may be convenient to compare the problem with that of a magnetic dipole moment placed in a magnetic field.

It is well known that a force exerted on the dipole placed in a magnetic field acts in the direction of the larger one when the strength of the magnetic field is inhomogeneous. The Gibbs free energy of the magnetic dipole moment in terms of natural variables T, H, for which its demagnetizing field is negligible, is defined as follows:

$$G(T, H) := \min_{M}[F(T, M) - MH]$$

$F(T, M), H, M$ are the Helmholtz free energy of the dipole with natural variables T, M, magnetic field, and magnetization per unit volume, respectively. With T fixed,

$$dG = dF - d(MH) = -MdH = -M\boldsymbol{\nabla}H \cdot d\boldsymbol{\xi}$$

Now we will show that $dG(T, H) < 0$, similar to the above discussion on that of the grand potential. When the dipole at $\boldsymbol{r} = \boldsymbol{\xi}$ is placed in the magnetic field $H(\boldsymbol{r})$, it has potential energy $-M(\boldsymbol{\xi})H(\boldsymbol{\xi})$. This means that under an infinitesimal displacement $\boldsymbol{\xi} \to \boldsymbol{\xi} + d\boldsymbol{\xi}$, the system must perform work $-d\left(M(\boldsymbol{\xi})H(\boldsymbol{\xi})\right)$ on the magnetic field in addition to the work performed on the external world. It is clear that this is equivalent to $-d\left(y(\boldsymbol{\xi})\mu(\boldsymbol{\xi})\right)$, when y, μ are replaced with M, H in the above discussion. Therefore, we see that when T is fixed, $dG(T, H) < 0$. When there is dissipation due to friction, assumed to be proportional to the velocity with the proportionality constant γ, the equation of motion for the dipole is given as follows:

$$\gamma\dot{\boldsymbol{\xi}} = M\boldsymbol{\nabla}H$$